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PATENT & TRADEMARK OFFICE

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Docket No. 003102-00092

JC474 U.S. PTO
10/042721
05/29/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pillai et al.
Serial No: Unassigned
Filed: May 29, 2002
For:
Group Art Unit: Unassigned
Examiner: Unassigned

#2/A

**AMINOCARBOXYLATE LIGANDS HAVING
SUBSTITUTED AROMATIC AMIDE MOIETIES**

919 Third Ave
New York, NY 10022

Commissioner for Patents
Washington, DC 20231

Adjustment date: 09/27/2002 TV0111
06/03/2002 AWONDAF1 00000121 08471556
~~03 FC:101 -740.00 UP~~
~~04 FC:102 84.00 GP~~

PRELIMINARY AMENDMENT

Sir:

Prior to the calculation of the fees due and the issuance of a first Office Action in this application, please amend the specification and claims as indicated below.

IN THE SPECIFICATION

Pursuant to 37 C.F.R. §§ 1.121(b)(1)(i) and (ii), *please delete the cross referencing information on p. 1, lines 4-6 and insert therefor the following paragraph:*

This application is a continuation of U.S. Application Serial No. 08/471,556, filed June 6, 1995, which is a divisional of U.S. Application Serial No. 08/010,909, filed January 29, 1993, which is a continuation-in-part of U.S. Serial No. 07/738,998, filed August 1, 1991. The subject matter of the parent applications are hereby incorporated by reference.

Please replace the paragraph beginning on page 5, line 33 to page 6, line 9 with the following paragraph:

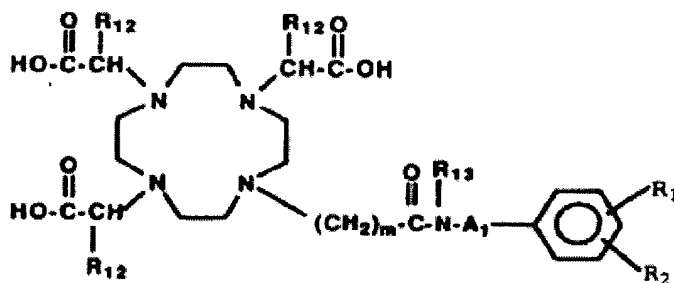
Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

The PTO did not receive the following listed item(s): *transmittal*

06/03/2002 AWONDAF1 00000121 08471556
~~03 FC:101 740.00 UP~~
~~04 FC:102 84.00 GP~~

Two general methods have been employed for making bifunctional chelates form chelating agents. In the first method one or more carboxylic acid groups of a polyaminopolycarboxylic acid chelator are activated by conversion to such activating groups as internal or mixed anhydrides, activated esters (e.g., p-nitrophenyl, N-hydroxysuccinimide, etc.) or with other derivatives known to those skilled in the art. The activated acid group is then added to the protein-chelator complex.

On page 11, please replace the first chemical formula with the following:



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Please replace the paragraph beginning on page 16, line 14 to page 17, line 5 with the following paragraph:

The methods of linking the bifunctional chelate to the antibody or antibody fragment are known in the art (Brechbiel, same reference as referred to hereinabove) and will depend primarily on the particular bifunctional chelate and secondarily on the antibody or fragment thereof. For example when the formula Ia compound is $R_1 = H$, $R_2 = -NCS$ or



one reacts 10 μL of a 5.0 mM aqueous solution of the formula I chelator with 0.5 mL of a 5.0 mg/mL monoclonal antibody (B72.3 purchaseable from Damon Biotech Corporation) in 50 mM Hepes buffer at pH 8.5. 16 μL of 1.5M aqueous triethylamine is added. After 2 hours reaction time, the monoclonal antibody is purified by dialysis. This procedure provides between 1 and 2 formula I chelator molecules bound to each monoclonal antibody.

Please replace the paragraph beginning on page 17, line 6 to line 27 with the following paragraph:

On page 31, please replace lines 30-31 with the following:

- On page 41, please replace lines 2-6 with the following:*

Data on Water Soluble Gd Complexes and Ions
Demonstrating the Enhancement of Relaxivity by
N-Hydroxyalkyl or N-alkyl-isophthalamide Groups and
by Aryl Groups or by Hydroxyalkyl or Alkylamido
Groups.

On page 42, please replace lines 7-8 with the following:

- A. N,N'-Bis(2-methylbutyl)-5-[[(phenylmethoxy)-
carbonyl]-amino]-1,3-benzenedicarboxamide

On page 42, please replace lines 26-28 with the following:

- B. N,N'-Bis(2-methylbutyl)-5-[methyl [(phenyl-
methoxy)carbonyl]amino]-1,3-benzende-
carboxamide

On page 49, please replace lines 16-18 with the following:

- B. 10-[N-(4-Nitrophenyl) acetamido]-1,4,7,10-
tetraazacyclododecane-1,4,7-triacetic acid,
monogadolinium salt

On page 57, please replace lines 16-19 with the following:

10-[2-[[3,5-Bis[(2-hydroxyethyl)amino]-
carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-
tetraazacyclododecane-1,4,7-triacetic acid-gadolinium
(III) complex

On page 57, please replace lines 21-22 with the following:

- A. N,N'-Bis(2-hydroxyethyl)-5-nitro-1,3-
benzenedicarboxamide

On page 58, please replace lines 1-2 with the following:

- B. N,N'-Bis(2-acetoxyethyl)-5-amino-1,3-
benzenedicarboxamide

On page 59, please replace lines 11-12 with the following:

- D. 5-[(Chloroacetyl)amino]-N,N'-bis(2-hydroxy-
ethyl)-1,3-benzenedicarboxomide

Please replace the paragraph beginning on page 59, line 13 to line 21 with the following paragraph:

A solution of N,N'-bis[2-(acetyloxy)ethyl]-5-[(chloroacetyl)amino]-1,3-benzenedicarboxamide (6.2 g, 14 mmol) in MeOH (20 mL) was treated with NaOMe (600 mg, 10.5 mmol). After 2 hours at room temperature, the mixture was neutralized with AG-50W-X2 (H⁺ form) resin. The resin was removed by filtration and the solution was evaporated to dryness to afford 4.8 g of crude material. An analytical sample of the title D product was crystallized from MeOH.

On page 59, please replace lines 29-32 with the following:

- E. 10-[2-[[3,5-Bis[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, monosodium salt.

On page 60, please replace lines 22-25 with the following:

- F. 10-[2-[[3,5-Bis[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-monogadolinium salt (VII).

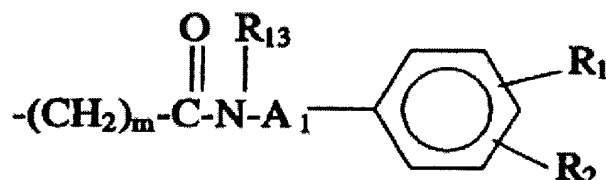
IN THE CLAIMS

Please cancel claims 5, 7-10, 13-38 and 40-50 without prejudice or disclaimer and amend the following claims:

1. (amended) A diagnostic agent comprising an aminocarboxylate ligand complexed with a paramagnetic metal ion wherein a nitrogen atom within said aminocarboxylate is substituted with a group comprising an aromatic amide containing at least one substitution on the aromatic ring, the substitution comprising a group of 3 or more non-hydrogen atoms.

2. (amended) The diagnostic agent of claim 1 wherein said substituted aromatic amide group is of the formula

I



wherein

A₁ is - (CH₂)_{m'} - or a single bond;

(CH₂)_m and (CH₂)_{m'} may independently be substituted with alkyl or hydroxyalkyl;

R₁ and R₂ are independently hydrogen,

alkyl, -NO₂, -NH₂, -NHC(=S)NHR₁₂, -C(=O)NR₃R₄, NR₃COR₉

where R₉ is C₄ - C₁₈ straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R₁ and R₂ must be other than hydrogen;

R₃ and R₄ are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R₁₂ is hydrogen, alkyl or hydroxyalkyl;

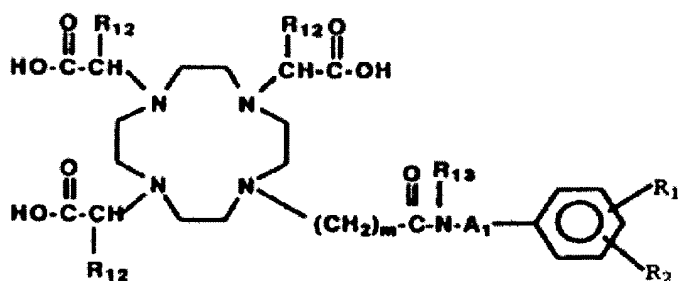
R₁₃ is hydrogen, alkyl or arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

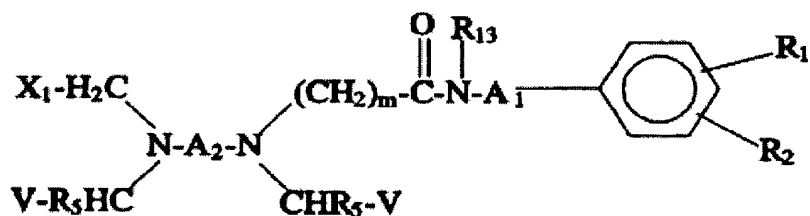
and multimeric forms thereof.

3. (amended) A diagnostic agent of claim 2 wherein said ligand is of the formula

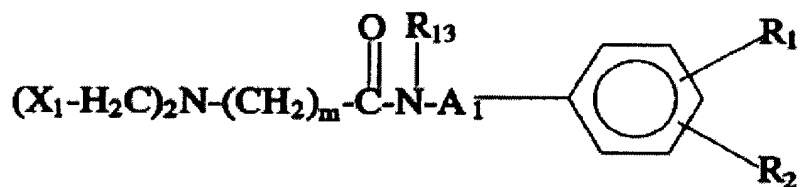
Ia



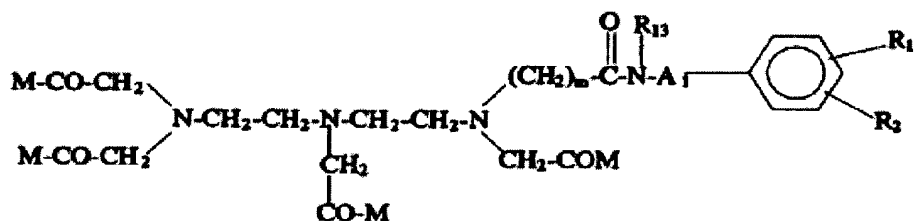
Ib



Ic



Id



wherein m, R₁₃, A₁, R₁, R₂, and R₁₂ are as defined in claim 2 and wherein

X_1 is $-COOY_1$, PO_3HY_1 or $-CONHOY_1$;

Y_1 is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A_2 is $-CHR_6-CHR_7-$, $-CH_2CH_2(ZCH_2-CH_2)_n-$,

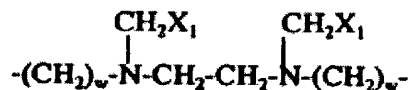
$$\begin{array}{c} N(CH_2X_1)_2 \\ | \\ -CH_2-CH-CH_2 \end{array} \quad \text{or} \quad \begin{array}{c} CH_2-CH_2-N(CH_2X_1)_2 \\ | \\ -CH_2-CH_2-N-CH_2-CH_2- \end{array}, \text{ wherein } X_1 \text{ is as defined above;}$$
 each R_5 is hydrogen or methyl;

R_6 and R_7 together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R_6 is a hydrogen atom and R_7 is a $-(CH_2)_p-C_6-H_4-W$ -protein where p is 0 or 1, W is $-NH-$, $-NHCOCH_2-$ or $-NHCS-$, protein represents a protein residue;

n is 1, 2 or 3;

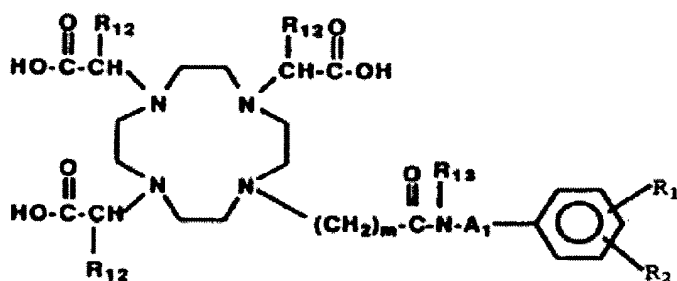
Z is an oxygen atom or a sulfur atom or the group NCH_2X_1 or $NCH_2CH_2OR_8$ wherein X_1 is as defined above and R_8 is C_{1-8} alkyl;

V is X_1 or is $-CH_2OH$, $-CONH(CH_2)_rX_1$ or $-COB$, wherein X_1 is as defined above, B is a protein or lipid residue, r is an integer from 1 to 12, or if R_5 , R_6 and R_7 are each hydrogen; then both V 's together form the group



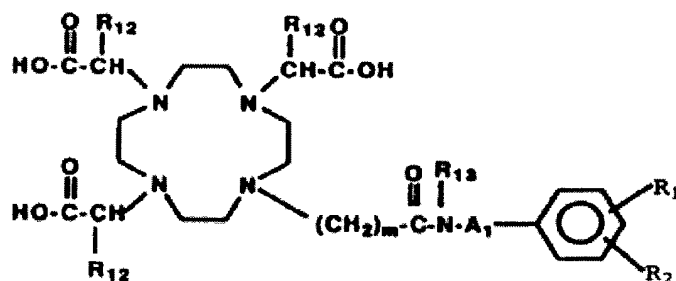
where X_1 is as above, w is 1, 2 or 3, provided that at least two of the substituents Y_1 represent metal ion equivalents of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83; from 1 to 4, advantageously 2 or 3, and preferably 2 M 's are $-OH$ and the balance independently are

6. (amended) A compound of the formula



and multimeric forms thereof.

11. (amended) A compound of the formula



having the name 10-[2-[[3,5-bis[(2,3-dihydroxypropyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid,

wherein

A₁ is -(CH₂)_m' - or a single bond;

(CH₂)_m and (CH₂)_m' may independently be substituted with alkyl or hydroxyalkyl;

R₁ and R₂ are each independently hydrogen,

alkyl, -NO₂, -NH₂, -NHCNHR₁₂, -C(=S)-NR₃R₄ and NR₃COR₉ where R₉ is C₄-C₁₈ straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R₁ and R₂ must be other than hydrogen;

R₃ and R₄ are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

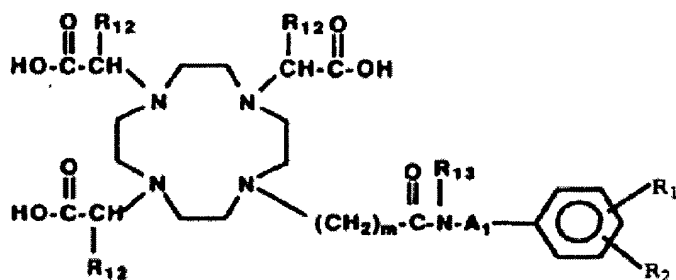
R₁₂ is hydrogen, alkyl or hydroxyalkyl;

R₁₃ is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

39. A complex or a pharmaceutically acceptable salt of a complex, of a metal atom and a metal chelating ligand having the formula



wherein

A_1 is $-(CH_2)_{m'}$ - or a single bond;

$(CH_2)_m$ and $(CH_2)_{m'}$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, $-C(=S)NR_3R_4$ and NR_3COR_9 where R_9 is C_4 - C_{18} straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

REMARKS

Original claims 5, 7-10, 13-38, and 40-50 were cancelled without prejudice or disclaimer.

Pursuant to 37 C.F.R. §§ 1.121(b), the current amendments to the specification and claims are also identified in marked up versions of the same attached hereto as Exhibit A and Exhibit B, respectfully, with all changes shown by conventional marking system or instructed changes. A copy of the pending claims is attached hereto as Exhibit C.

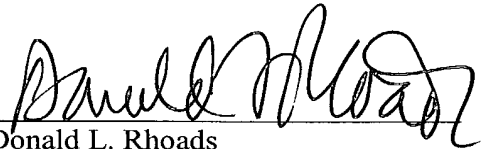
A check for \$824.00 has been submitted to cover the cost for filing this application with these amended claims. No additional fees are believed due. However, if any additional fees are necessary, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0540.

Applicants believe claims 1-4, 6, 11, 12, 39 are patentable and in condition for allowance. The claim is supported in the specification, and the original claims as filed.

Furthermore, Applicants are not aware of any prior art that has all of the elements of the claims or which in proper combination with other prior art would provide all of the elements of the claims.

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance and such action is earnestly solicited.

RESPECTFULLY SUBMITTED



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EXHIBIT A
MARKED UP VERSION OF AMENDMENT TO THE SPECIFICATION

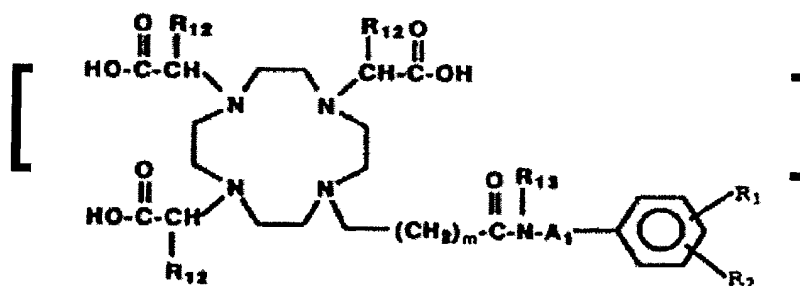
Page 1, lines 4-6:

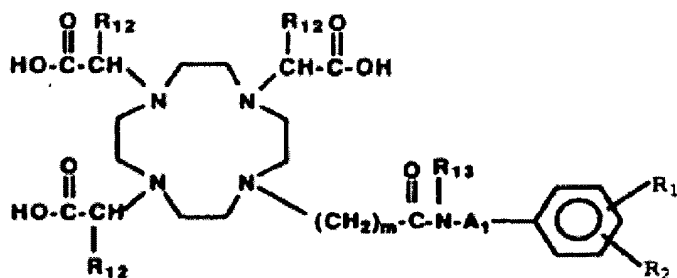
This application is [claiming] a continuation of U.S. Application Serial No. 09/410,984, filed October 1, 1999, which is divisional of U.S. Application Serial No. 08/856,657, filed May 15, 1997, now U.S. Patent No. 6,031,711, which claims priority from U.S. Provisional Application No. 60/017,609 filed May 15, 1996[, hereby incorporated by reference]. The subject matter of the parent applications are hereby incorporated by reference.

Page 5, line 33 to page 6, line 9:

Two general methods have been employed for making bifunctional chelates form chelating agents. In the first method one or more carboxylic acid groups of a polyaminopolycarboxylic acid chelator are activated by conversion to such activating groups as internal or mixed anhydrides, activated esters (e.g., [p-nitro phenyl] p-nitrophenyl, N-hydroxysuccinimide, etc.) or with other derivatives known to those skilled in the art. The activated acid group is then added to the protein-chelator complex.

Page 11, first chemical formula:





Page 16, line 14 to page 17, line 5:

The methods of linking the bifunctional chelate to the antibody or antibody fragment are known in the art (Brechtel, same reference as referred to hereinabove) and will depend primarily on the particular bifunctional chelate and secondarily on the antibody or fragment thereof. For example when the formula Ia compound is $R_1 = H$, $R_2 = -NCS$ or

$$\begin{array}{c} S \\ || \\ -NHCNHR_{12} \end{array}$$
 one reacts 10 μ L of a 5.0 mM aqueous solution of the formula I chelator with 0.5 mL of a 5.0 mg/mL monoclonal antibody (B72.3 purchaseable from Damon Biotech Corporation) in 50 mM Hepes buffer at pH 8.5. 16 μ L of 1.5M aqueous triethylamine is added. After 2 hours reaction time, the monoclonal antibody is purified by dialysis. This procedure provides between 1 and 2 formula I chelator molecules bound to each monoclonal antibody. Radioactive metal ion (for example ^{90}Y) can then be added to the monoclonal antibody-bound chelator by methods known in the art. For example, ^{90}Y as the $^{90}Y(III)(\text{acetate})_3(H_2O)_4$ approximate formula in aqueous solution) can be reacted with the monoclonal antibody-bound chelate in solutions where the concentration of each is between 10^{-5} and $10^{-7}M$ and the pH is 6. Dialysis against citrate is then used to purify the product.

Page 17, lines 6-27:

An alternative, and preferred method follows that described above, but substitutes the metal-chelate complex for the chelating ligand. To use this metal the metal chelate complex is

first made by reacting metal-oxide, -halide, -nitrate, -acetate, or the like with formula I chelator. For the chelator described above the acetate of ^{90}Y at $<10^{-6}\text{M}$ is reacted with the chelator at about 10^{-3}M at pH 6, the chelate complex is purified by ion exchange or reverse phase HPLC chromatography, and then reacted and then reacted with the monoclonal antibody described above for the chelator. The bifunctional, metal-containing, linked antibody is used in the following manner. A human or animal with a tumor to which the monoclonal antibody is specific is injected intravenously, subcutaneously, intraperitoneally or intralymphatically for example, with an aqueous solution of the ^{90}Y -formula I chelator-monoclonal antibody compound. This allows the radioactive metal ion to be directed to the tumor for which it is intended. The intravenous dosage used is 0.1 to 0.4 millicuries per kilogram of body weight.

Page 31, lines 30-31:

- A. N,N'-[b]Bis[2-([A]acetyloxy)-1-[(acetyloxy-methyl)-ethyl]-5-nitro-1, 3-benzenedicarboxamide

Page 41, lines 2-6:

Data on Water Soluble Gd Complexes and Ions
Demonstrating [T]the Enhancement of Relaxivity by
[N-Hydroxy-alkyl] N-Hydroxyalkyl or N-alkyl-isophthalamide
Groups and by Aryl Groups or by Hydroxyalkyl or Alkylamido
Groups.

Page 42, lines 7-8:

- A. [N,N'-bis(2-Methylbutyl)] N,N'-Bis(2-methylbutyl)-5-[[(phenylmethoxy)-carbonyl]-amino]-1,3-benzenedicarboxamide

Page 42, lines 26-28:

- B. [N,N'-bis(2-Methylbutyl)] N,N'-Bis(2-methylbutyl)-5-[methyl [(phenyl-methoxy)carbonyl]amino]-1,3-benzende-carboxamide

Page 49, lines 16-18:

- B. 10-[N-([4 Nitrophenyl] 4-Nitrophenyl) acetamido]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt

Page 57, lines 16-19:

10-[2-[[3,5-[b]Bis[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid-gadolinium (III) complex

Page 57, lines 21-22:

- A. N,N'-[b]Bis(2-hydroxyethyl)-5-nitro-1,3-benzenedicarboxamide

Page 58, lines 1 and 2:

- B. N,N'-[b]Bis(2-acetoxyethyl)-5-amino-1,3-benzenedicarboxamide

Page 59, lines 10-11:

- D. 5-[[c]Chloroacetyl]amino]-N,N'-bis(2-hydroxyethyl)-5-amino]-1,3-benzenedicarboxomide

Page 58, lines 13-21:

A solution of N,N'-bis[2-(acetyloxy)ethyl]-5-[(chloroacetyl)amino]-1,3-benzenedicarboxamide (6.2 g, 14 mmol) in MeOH (20 mL) was treated with NaOMe (600 mg, 10.5 mmol). After 2 hours at room temperature, the mixture was neutralized with AG-50W-X2 ([H⁺]H⁺ form) resin. The resin was removed by filtration and the solution was evaporated to dryness to afford 4.8 g of crude material. An analytical sample of the title D product was crystallized from MeOH.

Page 59, line 28-31:

- Page 60, lines 22-25:*

- F. 10-[2-[[[3,5-[b]Bis[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-monogadolium salt (VII).

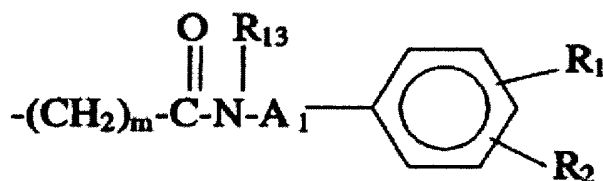
EXHIBIT B

MARKED UP VERSION OF THE AMENDED CLAIMS

1. (amended) A diagnostic agent comprising an aminocarboxylate ligand complexed with a paramagnetic metal ion wherein a nitrogen atom within said aminocarboxylate is substituted with a [substituted aromatic amide] group comprising an aromatic amide containing at least one substitution on the aromatic ring, the substitution comprising a group of 3 or more non-hydrogen atoms.

2. (amended) The diagnostic agent of claim 1 wherein said substituted aromatic amide group is of the formula

I



wherein

A₁ is - (CH₂)_m' - or a single bond;

(CH₂)_m and (CH₂)_m' may independently be substituted with alkyl or hydroxyalkyl;

R₁ and R₂ are independently hydrogen,

alkyl, -NO₂, -NH₂, -NHCNHR₁₂, [NCS,] -C(=O)-NR₃R₄, NR₃COR₉

where R₉ is C₄ - C₁₈ straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R₁ and R₂ must be other than hydrogen;

R₁₂ is hydrogen, alkyl or hydroxyalkyl;

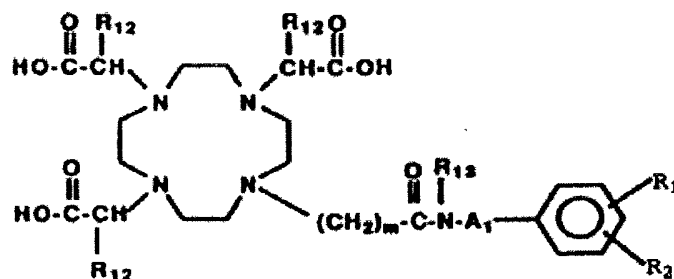
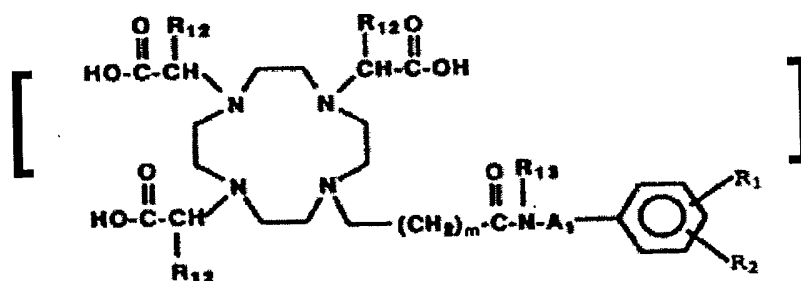
R₁₃ is hydrogen, alkyl or arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently [1] 0 to 5;

and multimeric forms thereof.

3. (amended) A diagnostic agent of claim 2 wherein said ligand is of the formula

Ia



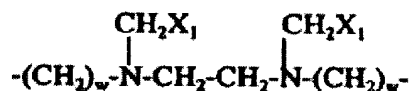
$$\begin{array}{c} \text{X}_1\text{-H}_2\text{C} \quad \quad \quad (\text{CH}_2)_m\text{-}\overset{\text{O}}{\overset{\text{R}_{13}}{\parallel}}\text{C-N-A}_1\text{-}\text{C}_6\text{H}_4\text{-}\overset{\text{R}_1}{\text{C}_6\text{H}_4}\text{-}\overset{\text{R}_2}{\text{C}_6\text{H}_4} \\ \quad \quad \quad \diagdown \quad \quad \quad \diagup \\ \quad \quad \quad \text{N-A}_2\text{-N} \\ \quad \quad \quad \diagup \quad \quad \quad \diagdown \\ \text{V-R}_3\text{HC} \quad \quad \quad \text{CHR}_4\text{-V} \end{array}$$
$$(X_1-H_2C)_2N-(CH_2)_m-\overset{\overset{O}{\parallel}}{C}-N(\overset{\overset{R_{13}}{\mid}}{A})-I-\text{C}_6\text{H}_4-\begin{matrix} R_1 \\ R_2 \end{matrix}$$
$$\begin{array}{c} \text{M-CO-CH}_2 \\ \text{M-CO-CH}_2 \end{array} \text{N-CH}_2\text{-CH}_2\text{-N-CH}_2\text{-CH}_2\text{-N} \begin{array}{c} \text{(CH}_2\text{)}_m\text{-C(=O)-N-A-} \\ \text{CH}_2\text{-COM} \end{array} \text{C}_6\text{H}_4 \begin{array}{c} \text{R}_1 \\ \text{R}_2 \end{array}$$
$$\begin{array}{c} \text{N}(\text{CH}_2\text{X}_1)_2 \\ | \\ -\text{CH}_2-\text{CH}-\text{CH}_2 \end{array} \quad \text{or} \quad \begin{array}{c} \text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{X}_1)_2 \\ | \\ -\text{CH}_2-\text{CH}_2-\text{N}-\text{CH}_2-\text{CH}_2- \end{array}, \text{ wherein } \text{X}_1 \text{ is as defined above;}$$

R₆ and R₇ together represent a trimethylene group or a tetramethylene group or

n is 1, 2 or 3;

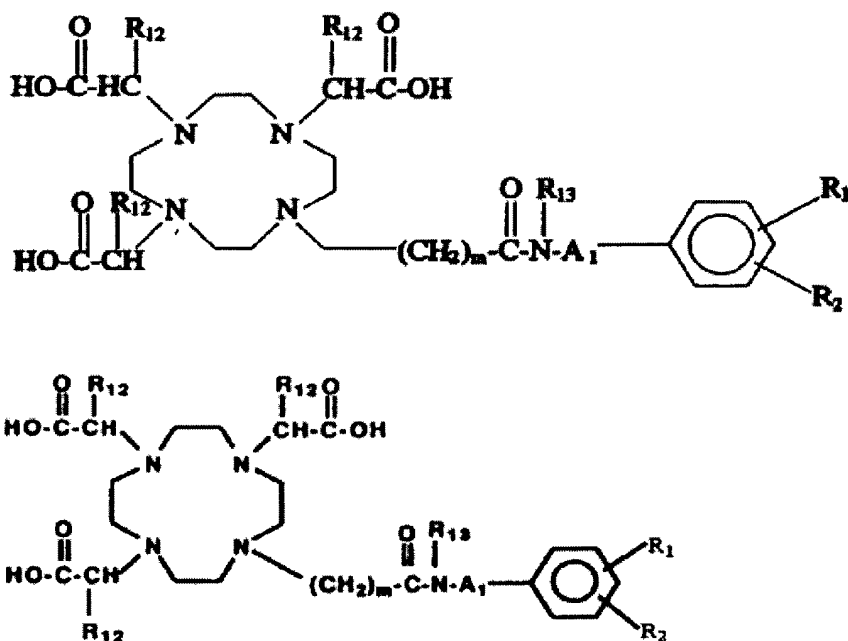
Z is an oxygen atom or a sulfur atom or the group NCH_2X_1 or $\text{NCH}_2\text{CH}_2\text{OR}_8$ wherein X_1 is as defined above and R_8 is C_{1-8} alkyl;

V is X_1 or is $-CH_2OH$, $-CONH(CH_2)_rX_1$ or $-COB$, wherein X_1 is as defined above, B is a protein or lipid residue, r is an integer from 1 to 12, or if R_5 , R_6 and R_7 are each hydrogen; then both V's together form the group



where X_1 is as above, w is 1, 2 or 3, provided that at least two of the substituents Y_1 represent metal ion equivalents of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83; from 1 to 4, advantageously 2 or 3, and preferably 2 M's are -OH and the balance independently are -OR₁₀, -NH₂, -NHR₁₀ and/or NR₁₀R₁₀' wherein R₁₀ and R₁₀' are selected from an organic alkyl radical of up to 18 carbon atoms which may be substituted.

6. (amended) A compound of the formula



wherein

A₁ is -(CH₂)_{m'} - or a single bond;

(CH₂)_m and (CH₂)_{m'} may independently be substituted with alkyl or hydroxyalkyl;

R₁ and R₂ are each independently hydrogen,

alkyl, -NO₂, -NH₂, -NHCNHR₁₂, [NCS₂], -C(=O)NR₃R₄ and NR₃COR₉ where R₉ is C₄-C₁₈

straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R₁ and R₂ must be other than hydrogen;

R₃ and R₄ are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

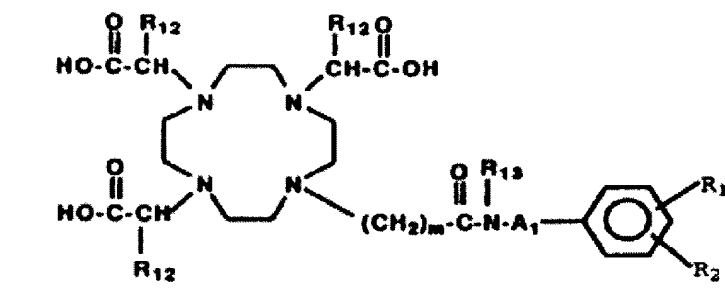
R₁₂ is hydrogen, alkyl or hydroxyalkyl;

R₁₃ is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently [1] 0 to 5;

and multimeric forms thereof.

11. (amended) A compound of the formula [of claim 6]



having the name 10-[2-[[3,5-bis[(2,3-dihydroxypropyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid,

wherein

A_1 is $-(\text{CH}_2)_m-$ or a single bond;

$(\text{CH}_2)_m$ and $(\text{CH}_2)_m'$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCNHR}_{12}$, $-\text{C}(=\text{S})-\text{NR}_3\text{R}_4$ and NR_3COR_9 where R_9 is C_4 - C_{18} straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

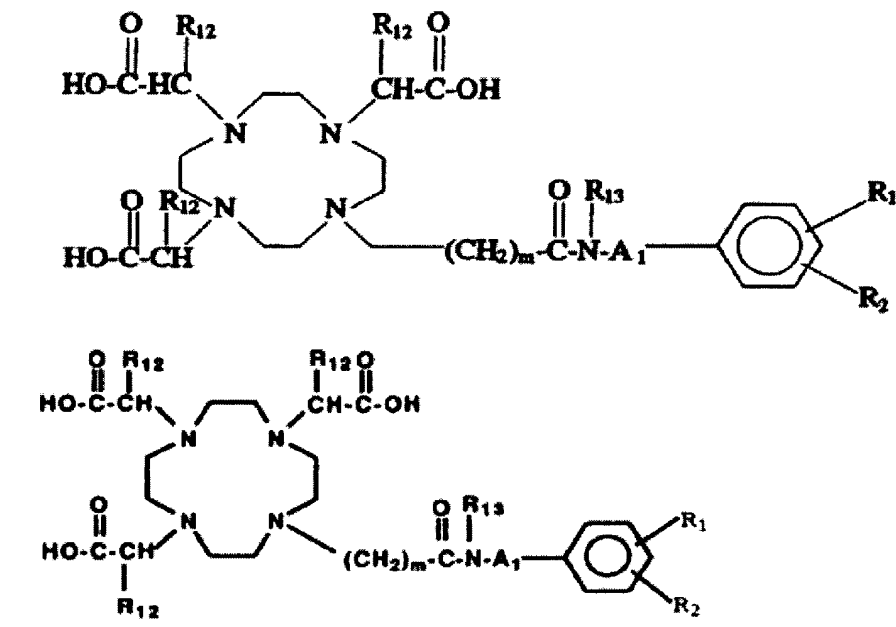
R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

39. A complex or a pharmaceutically acceptable salt of a complex, of a metal atom and a metal chelating ligand having the formula

I



wherein

A_1 is $-(CH_2)_m-$ or a single bond;

$(CH_2)_m$ and $(CH_2)_m'$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, $[NCS]$, $-C(=O)NR_3R_4$ and NR_3COR_9 where R_9 is C_4-C_{18}

straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

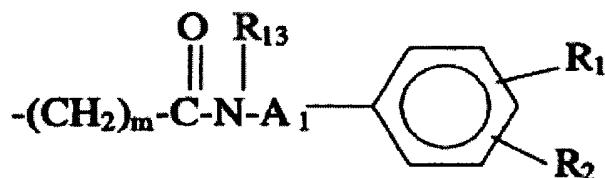
R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently [1] 0 to 5;

and multimeric forms thereof.

EXHIBIT C**PENDING CLAIMS**

1. A diagnostic agent comprising an aminocarboxylate ligand complexed with a paramagnetic metal ion wherein a nitrogen atom within said aminocarboxylate is substituted with a group comprising an aromatic amide containing at least one substitution on the aromatic ring, the substitution comprising a group of 3 or more non-hydrogen atoms.
2. The diagnostic agent of claim 1 wherein said substituted aromatic amide group is of the formula

I

wherein

A_1 is $-(\text{CH}_2)_{m'}$ - or a single bond;

$(\text{CH}_2)_m$ and $(\text{CH}_2)_{m'}$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are independently hydrogen,

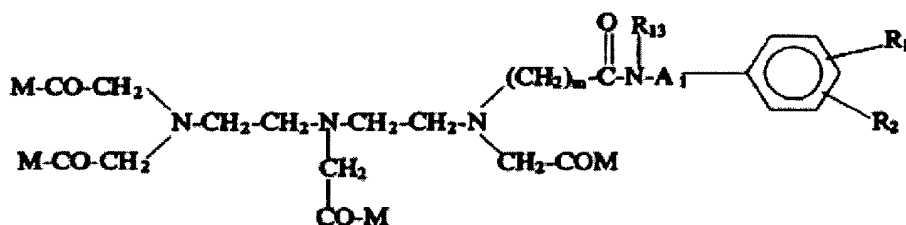
alkyl, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHC}(=\text{S})\text{NHR}_{12}$, $-\text{C}(=\text{O})\text{NR}_3\text{R}_4$, NR_3COR_9 ,

where R_9 is $\text{C}_4 - \text{C}_{18}$ a straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;



Id

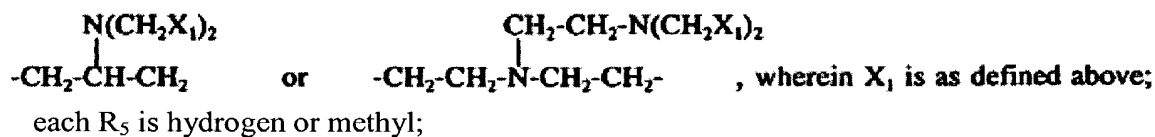


wherein m, R₁₃, A₁, R₁, R₂, and R₁₂ are as defined in claim 2 and wherein

X₁ is -COOY₁, PO₃HY₁ or -CONHOY₁;

Y₁ is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A₂ is -CHR₆-CHR₇-, -CH₂CH₂(ZCH₂-CH₂)_n-,

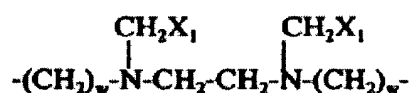


R₆ and R₇ together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R₆ is a hydrogen atom and R₇ is a -(CH₂)_p-C₆-H₄-W-protein where p is 0 or 1, W is -NH-, -NHCOCH₂- or -NHCS-, protein represents a protein residue;

n is 1, 2 or 3;

Z is an oxygen atom or a sulfur atom or the group NCH₂X₁ or NCH₂CH₂OR₈ wherein X₁ is as defined above and R₈ is C₁₋₈ alkyl;

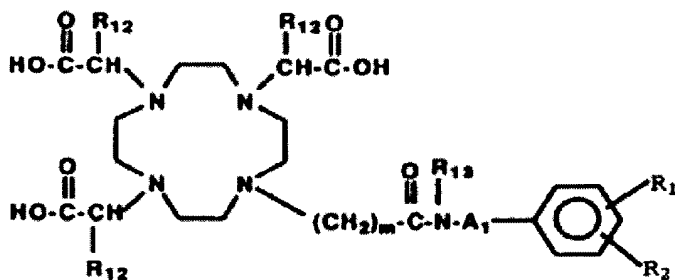
V is X_1 or is $-\text{CH}_2\text{OH}$, $-\text{CONH}(\text{CH}_2)_rX_1$ or $-\text{COB}$, wherein X_1 is as defined above, B is a protein or lipid residue, r is an integer from 1 to 12, or if R_5 , R_6 and R_7 are each hydrogen; then both V's together form the group



where X_1 is as above, w is 1, 2 or 3, provided that at least two of the substituents Y_1 represent metal ion equivalents of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83; from 1 to 4, advantageously 2 or 3, and preferably 2 M's are $-\text{OH}$ and the balance independently are $-\text{OR}_{10}$, $-\text{NH}_2$, $-\text{NHR}_{10}$ and/or $\text{NR}_{10}\text{R}_{10}'$ wherein R_{10} and R_{10}' are selected from an organic alkyl radical of up to 18 carbon atoms which may be substituted.

4. The diagnostic agent of claim 1 wherein said paramagnetic metal ion is gadolinium.

6. A compound of the formula



wherein

A_1 is $-(\text{CH}_2)_m-$ or a single bond;

$(\text{CH}_2)_m$ and $(\text{CH}_2)_m'$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCNHR}_{12}$, $-\text{C}(=\text{S})\text{NR}_3\text{R}_4$ and NR_3COR_9 where R_9 is C_4 - C_{18} straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

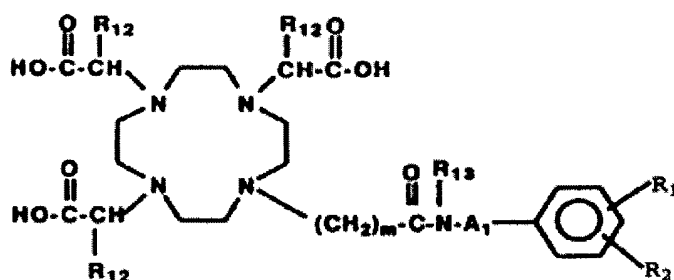
R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

11. (amended) A compound of the formula



having the name 10-[2-[[3,5-bis[(2,3-dihydroxypropyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid,

wherein

A_1 is $-(\text{CH}_2)_m$ - or a single bond;

$(\text{CH}_2)_m$ and $(\text{CH}_2)_{m'}$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCNHR}_{12}$, $-\text{C}(=\text{S})\text{NR}_3\text{R}_4$ and NR_3COR_9 where R_9 is C_4 - C_{18} straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

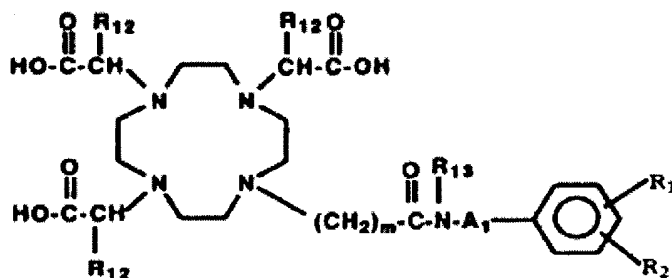
R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

12. The gadolinium complex of the compound of claim 11.

39. A complex or a pharmaceutically acceptable salt of a complex, of a metal atom and a metal chelating ligand having the formula



wherein

A_1 is $-(CH_2)_{m'}$ - or a single bond;

$(CH_2)_m$ and $(CH_2)_{m'}$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, $-C(=S)NR_3R_4$ and NR_3COR_9 where R_9 is C_4 - C_{18} straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;
and multimeric forms thereof.